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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,853	ANDREWS ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-28* is/are pending in the application.

4a) Of the above claim(s) *21,22 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-20,23-25,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 5/28/04, has been entered. Claims 1-8 and 10-28 are pending. Claims 1-8, 10, 12-19, 23, 25 and 28 have been amended. Claim 9 has been cancelled. Claims 21, 22 and 26 are withdrawn. Claims 1-8, 10-20, 23-25, 27 and 28 are under current examination.

Election/Restrictions

Claims 21, 22 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Information Disclosure Statement

Applicants' Information Disclosure Statements, filed 5/04/04 and 6/22/04 have been considered.

Claim Objections

The prior objection to claims 2-10 and 28 are withdrawn in view of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 101

The prior rejection of claims 1-10 and 23 under 35 U.S.C. 101 is withdrawn in view of Applicants' amendment to the claims with regard to the recitation of "isolated".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 23-25, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells and methods for preparing cells that express Oct4, wherein the cell comprises either (i) at least one part of the cytoplasm derived from an embryonal teratocarcinoma cell, or (ii) a cytoplast from a teratocarcinoma cell, and the cell has its nucleus obtained from a differentiated somatic cell and only contains the genome derived from the differentiated somatic cell, does not reasonably provide enablement for cells and methods of making cells which possess at least one pluripotent characteristic, which includes the ability to differentiate into at least two selected tissue types. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that *Oct4* expression is well-known as an indicator of pluripotency. Applicants provide Brehm *et al.*, Flasza *et al.* (who discuss a cell possessing at least one pluripotential characteristic, as evidenced by the expression of Oct4 , and thus Flasza have shown that PEG-mediated fusion of murine EC cell line P19 with a human T-lymphoma cell line resulted in reprogramming of the human somatic cell to exhibit pluripotential characteristics, such as Oct4 and Sox2 expression. Applicants argue further, that with regard to Monk & Holding (cited in the prior Office action), that Oct4 is expressed in human tumors and does not denigrate Oct4 as a pluripotency marker, contrary to the Examiner's speculation. Further, Applicants argue that it is widely considered that, during the development of certain malignancies, the malignant cells re-establish their pluripotency and point to Monk & Holding for support. Applicants argue that the Examiner is not at liberty to dismiss the significance of genes, such as Oct4, that are expressed in a pluripotent cells, merely because those genes are also expressed in a tumor cell. Applicants submit that the pluripotency of the cells in the specific examples cannot be justifiably denied by saying that Oct4 is present in certain tumor cells. See pp. 9-10 of the Response.

Brehm *et al.* have been considered. Flasza *et al.* was not provided in the IDS filed 6/22/04, nor with the Response filed 5/28/04 and therefore arguments with regard to Flasza *et al.* cannot be considered. Applicants' arguments are not found to be persuasive. The Examiner maintains that although Oct-4 is expressed by

pluripotent cells, the mere expression of Oct-4 does not provide sufficient teaching to conclude that a particular cell is indeed pluripotent. The Examiner agrees that, as Monk and Holding teach, Oct4 is expressed in human tumors, and that in certain malignancies, cells re-establish their pluripotency does not denigrate Oct4 as a pluripotency marker. The indication that cells (which may or may not be pluripotent) can express Oct4 provides evidence that mere expression of Oct4 may not indicate pluripotency. Thus, other markers or characteristics must be present in the instantly claimed cells in order to establish their pluripotency. For example, Eiges and Benvenisty [**FEBS Letters**, 529:135-141 (2002)] state, with regard to pluripotent cells:

> "They are characterized by a unique repertoire of cell surface molecules, including stage-specific embryonic antigens (SSEA), and the activity of specific enzymes, such as alkaline phosphatase and telomerase. Although neither of these markers is completely cell specific, their presence as a group is associated with the undifferentiated state of the cells. In addition, a short list of molecular markers, which are rapidly down-regulated upon differentiation is available for mouse ES cells. It includes several transcription factors like Rex1, Genesis, GBX2, Oct4, UTF2, Pem and L17, which are members of well-known gene families and that are also expressed by the ICM of the blastocyst. *Unfortunately, none of them is exclusively expressed by pluripotent cells and can be found in other cell types in the soma.*" See p. 135, 2nd column, first full ¶. Emphasis added.

Thus, although Oct4 may be expressed by pluripotent cells, the sole expression of Oct4 is not sufficient to establish the pluripotency of a cell. The teachings and guidance provided by the specification fail to establish that the cells of the invention are pluripotent. The specification shows one example of

reprogramming in mouse thymocytes, as evidenced by the expression of Oct4, but no further analysis of the cells is conducted.

Applicants argue that, with regard to the teachings in the specification that the human EC cell line TERA1 appeared unable to reprogram mouse thymocytes, one of ordinary skill in the art would appreciate that the formation of hybrids between two cells of the same species has low efficiency, and that hybrids from two different species may occur at even lower frequency. Thus, Applicants conclude that it would not be unexpected that hybrids between a particular pair of cell types may occur at a higher or lower frequency than another pair of cell types and that cell-cell fusion is a genetically controlled event and may be subject to the same variations as any other Mendelian trait in the genome. Thus, the 2102Ep cytoplasm may appear to reprogram partner thymocytes more readily than the TERA1 cytoplasm. See p. 10, 2nd ¶. Applicants further argue that an assay used to detect reprogramming should be robust in order to compensate for the paucity of fused, and potentially reprogrammed and pluripotent, cells, and that PCR has a finite capacity to detect rare events in gene expression, and that the detection of Oct4 expression in fusions between 2102Ep cells and mouse thymocytes may have been just above a dateable limit. Applicants argue that other means of measuring reprogramming and pluripotency might show that TERA1 was equally capable of reprogramming thymocytes in fusions. See pp. 10-11 of the Response.

This is not found to be persuasive. Firstly, the arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that hybrid formation between different species of cells would occur at a lower frequency, to support Applicants' conclusion that the TERA1 cytoplasm would be more inefficient at forming fusions than the 2102Ep cytoplasm. Nor have Applicants' provided any specific evidence with regard to "other means" of measuring reprogramming and pluripotency. The prior rejection is based upon the specification's showing of one example of putative reprogramming, which the specification and Applicants argue is evidenced by the expression of Oct4 in the resulting heterokaryons. As stated *supra*, this fails to be sufficient indicator to show that the cells are indeed pluripotent, as presently claimed.

Applicants' arguments with regard to the generation of a nuclear transfer (NT) unit, and the requirement of activation are found to be persuasive because the heterokaryons, as instantly claimed, would not require activation. Applicants' arguments to claim 5, and the expression of Oct-4 in the NT unit are found to be persuasive, because it is acknowledged that the cell of claim 5 would not be considered an NT unit.

Accordingly, it is reiterated that the specification fails to provide specific teachings or guidance to show that the methods of the claimed invention would,

indeed, produce cells that are pluripotent. The specification's showing of mere Oct4 expression in the fused heterokaryons is not enabling, as shown *supra*, that the mere expression of Oct4 is not necessarily indicative of pluripotency. The specification fails to teach that the cells of the claimed invention express specific cell surface markers that are indicative of pluripotent cells, that the cells of the invention show high levels of telomerase activity, are methylated in a pattern characteristic of pluripotent cells, or are able to induce tumors when introduced in an animal, as required by the claims. As such, the specification fails to provide an enabling disclosure for the generation and use of the claimed cells, and therefore, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-15, 20, 23-25 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The prior rejection of claim 1 as indefinite is maintained for reasons of record. Applicants argue that the Examiner's objection is not well-founded because one of

skill in the art would understand what is meant by "the ability" to differentiate into at least two selected tissue types in the context of pluripotent cells. Applicants point to the specification to support that one of skill in the art would understand this term, and refer to the Examiner to the Thomson Patent (5,843,780). This is not persuasive. The claim is unclear the recitation of "the ability" describes a latent property and thus, the metes and bounds of this term are unclear. "The ability" of the cells to differentiate into at least two selected tissue types encompasses cells which do differentiate into two tissue types, and those which do not differentiate into two tissue types. Thus, it is unclear what property Applicants are attempting to claim. The prior rejection with regard to the term "derived from" being unclear is rendered moot in view of Applicants' amendment to the claims. Claims 2-8, 10-15, 20, 23-25 and 27 depend from claim 1.

The prior rejection of claim 3 as indefinite is maintained for reasons of record. Applicants' arguments state that a skilled person would appreciate that the claimed cell possess the property to be able to proliferate in culture in an undifferentiated state, and whether this property is exhibited depends upon the conditions in which the cell is maintained. This is not found to be persuasive. As stated previously, the term "the capacity" is found to be indefinite and unclear because the metes and bounds of the term, and thus the claim, are not defined. Indeed, Applicants' arguments support this rejection, because the term "the capacity" encompasses cells which are undifferentiated and those which would be differentiated.

The prior rejection of claim 5, as indefinite, is withdrawn because the claim does not recite the term "the capacity".

The prior rejection of claim 9 is rendered moot in view of the cancellation of this claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 1-12, 20, 23-25 and 27 under 35 U.S.C. 102(b) as being anticipated by Thomson is maintained for reasons of record.

Applicants argue that Thomson do not teach the claimed invention because although EC cells have been shown to share many features with ES cells, EC cells are a separate entity with distinguishable features, for example, mutations that result in the malignant phenotype of EC cells. Further, Applicants argue that the ES cells taught by Thomson are derived from the ICM of a developing embryo, and have no relation to the embryonal carcinoma cells of the invention. Finally, Applicants argue that Thomson's cells do not have at least part of the cytoplasm derived from an EC cell. See p. 15 of the Response.

This is not persuasive. The claims as amended require "at least part" of the cytoplasm of the cell derived from an EC cell (see part (i) of claim 1) and the nucleus obtained from a differentiated somatic cell that contains the genome of only the differentiated cell. Thus, "at least a part" of the cytoplasm from an EC cell would be anticipated by cytoplasm from a cell, which has some parts in common with an EC cell. Steadman's defines cytoplasm as, "The substance of a cell, exclusive of the nucleus, which contains various organelles within a colloidal protoplasm." Thus, the ES cells of Thomson anticipate the claimed invention because the cytoplasm of the ES cells would not be distinguishable from "at least part" of a cytoplasm from an EC cell. For example, ES and EC cells' cytoplasms would have organelles in common. Furthermore, with regard to Applicants' arguments that Thomson's cells are not derived from the same source, it is reiterated that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Note further that the limitation of the nucleus obtained from a differentiated somatic cell and contains only the genome from the differentiated cell, as currently amended, does not obviate the prior rejection because the genome of a cell, as defined by Steadman's Medical Dictionary, is, "A complete set of chromosomes derived from one parent, or the total gene complement of a set of

chromosomes." Thus, a genome from a differentiated cell versus the genome of an undifferentiated cell would be the same, as both cells would contain a complete set of chromosomes, or a total gene complement. Further, with regard to Applicants' arguments that EC cells would have distinguishable features from Thomson's ES cells due to mutations in EC cells, it is noted that the claims do not specifically recite that the nucleus does not contain mutations, and it is recognized in the art that as cells divide and grow they obtain mutations, from, for example, recombination. Accordingly, it is maintained that Thomson anticipate the claims.

The prior rejection of claims 1, 4, 6, 11, 20, 23, 24, 25 and 27 under 35 U.S.C. 102(b) as being anticipated by Warejcka *et al.* is maintained for reasons of record.

Applicants argue that Warejcka do not anticipate the claimed invention because the deletion of the term "derived from" renders the prior rejection moot, as the claims now require that the cytoplasm come from an EC cell and a nucleus with a genome from a differentiated somatic cell. Further, Applicants argue that Warejcka's cells do not anticipate the claimed invention because the cells are mesodermal stem cells, and thus, these cells are limited to differentiation along a pathway that gives rise to mesodermal derivatives. Further, these cells are not pluripotent and would not be expected to express Oct4, or any markers characteristic of pluripotent cells. Furthermore, the cells, as taught by Warejcka

would not be expected to give rise to other two germ layers. See Response, pp. 16-17.

This is not found to be persuasive. The claims, as currently amended, are anticipated by Warejcka because 1) the claims as amended require "at least part" of the cytoplasm of the cell derived from an EC cell (see part (i) of claim 1) and the nucleus obtained from a differentiated somatic cell that contains the genome of only the differentiated cell. Thus, "at least a part" of the cytoplasm from an EC cell would be anticipated by cytoplasm from a cell, which has some parts in common with an EC cell, for example, the stem cells as taught by Warejcka. Thus, the stem cells of Warejcka anticipate the claimed invention because the cytoplasm of the stem cells would not be distinguishable from "at least part" of a cytoplasm from an EC cell. For example, cytoplasm of both the stem cells of Warejcka and EC cells would have organelles in common. Furthermore, it is noted that the rejection is not directed to particular claims that Applicants appear to address in the Response. The claims that are rejected by Warejcka are not directed to specific embodiments such as the expression of SSEA-3, SSEA-4, TRA-1-60 or Oct4. See p. 17, 1st ¶ of the Response. The cells of Warejcka are not distinguishable from the instantly claimed cells, the genome of the cells would not be distinguishable from the genome of a differentiated somatic cell, as the genome refers to a complete set of chromosomes (see *supra*). Warejcka teach the claimed invention because the cells only require the ability to differentiate into two selected cell types, which is taught to be

cartilage nodules, endothelial cells, adipocytes, smooth muscle cells, and putative cardiomyocytes. Note that claims 24, 25 and 27 recite the intended use of the cells, which does not impart patentable weight. See prior Office action, p. 17. Accordingly, Warejcka anticipate the claimed invention.

The prior rejection of claims 1-8, 10-12, 20, 23-25 and 27 under 35 U.S.C. 102(b) as being anticipated by Pera *et al.* is maintained for reasons of record.

The claims, as currently amended, recite an isolated cell comprising a single nucleus wherein the cell possesses at least one pluripotential characteristic, which includes the ability to differentiate into at least two selected tissue types, whyerein the cell comprises (i) at least part of the cytoplasm from an embryonal carcinoma cell or (ii) a cytoplast from an embryonal carcinoma cell, wherein the cell has it nucleus obtained from a differentiated somatic cell and contains a genome only from the differentiated cell.

Applicants argue that claim 1 as now amended obviates the prior rejection because the Examiner's prior comments with regard to "derived from" are rendered moot because the cells from Pera do not comprise cytoplasm from an embryonal carcinoma cell with a nucleus with a genome from a differentiated somatic cell. See p. 17-18 of the Response. Applicants further argue that the EC cell as taught by Pera was not obtained by combining a cytoplasmic part of an EC cell and a nucleus of a differentiated somatic cell, but arose from a malignant transformation which

produced the cell line GCT27. Thus, Applicants argue that the cells of the instant invention are distinguishable from those taught by Pera because tumors are created due to many mutations that accumulate during the development of malignancy, and while some of the mutations are commonly observed in certain tumors, the causes of these mutations are not well-known for individual tumors. Thus, the nucleus of the tumorigenic EC cell taught by Pera cannot be used to anticipate the claimed invention, because the nucleus of a somatic cell would not have the accumulated mutations of the somatic cell. Further, Applicants argue that it is generally believed that tumors originate from germ cells in both their gonadal and extra-gonadal forms, and that germ cells, by definition, are not somatic cells. See p. 18, 2nd ¶ of the Response.

The prior rejection is maintained because the claims as amended state that the isolated cell has at least part of the cytoplasm derived from an embryonal carcinoma and the nucleus is obtained from a differentiated somatic cell and contains only a genome from the differentiated somatic cell. The genome of a cell, as defined by Steadman's Medical Dictionary, is, "A complete set of chromosomes derived from one parent, or the total gene complement of a set of chromosomes." Thus, a genome from a differentiated cell versus the genome of an undifferentiated cell would be the same, as both cells would contain a complete set of chromosomes, or a total gene complement. Thus, the human teratoma cells, as taught by Pera, would anticipate the claims because they would have a genome that would be the

same as a differentiated cell. Further, one of skill in the art would not be able to distinguish between the cells as taught by Pera, and the claimed cells, as the cytoplasm of the cells taught by Pera would be from an embryonal carcinoma cell. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Claims 24, 25 and 27 recite the intended use of the cells, and it is reiterated that the intended use does not impart patentable weight. See *supra*.

Accordingly, Pera anticipate the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt
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